COMMENTS AND RESPONSES

Response to Comment on: Stefanovski et al. Estimating Hepatic Glucokinase Activity Using a Simple Model of Lactate Kinetics. Diabetes Care 2012;35:1015–1020

We are pleased to respond to the comment by Loranne Agius (1) relating to our recent article in *Diabetes Care* (2). Overall, we are in agreement with Agius that further well-designed studies are needed to validate the underlying assumptions of the model. For that purpose, we are already performing studies that will help clarify these questions. Nevertheless, a point was raised in Agius's letter that we wanted to comment on further.

As stated by Agius, one possible explanation for the 50% difference in our estimates of glucokinase activity and that of Iozzo et al. (3) may be a result of the differences in average population estimates of glucokinase flux in the two studies. Indeed, while in our cohort we had both female and male participants, the cohort in the study by Iozzo et al. was mostly composed of males who were on average 10 years younger. In addition and as explained in our article, we considered the difference in the experimental protocols used to estimate glucokinase flux as the one of the major reasons for the 50% difference. Iozzo et al. were using a 40 $mU \cdot m^2 \cdot min^{-1}$ constant infusion of insulin for a period of 120 min while during the frequently sampled intravenous glucose tolerance test (FSIGT), insulin was allowed to freely fluctuate (3). On average, plasma insulin peaks twice (once after the glucose bolus and once after the secretagogue bolus) during FSIGT protocol. These peaks in plasma insulin are short-lived, and insulin returns to basal levels within 20 min. Thus, the constantly elevated insulin combined with higher glucose infusion during the euglycemic clamp in the study by Iozzo et al. may have synergistically resulted in activation of glucokinase above the activation level observed during FSIGT because excursions of insulin above basal are few and short-lived. Furthermore, the above justification clarifies our stand that during FSIGT the changes in insulin happen very rapidly and as such do not influence glucokinase activity, while during the euglycemic-hyperinsulinemic protocol this is highly likely.

In summary, we believe that the difference in populations studied between Iozzo et al.'s study and ours combined with the differences in the experimental protocols—especially in regards to plasma insulin level—may explain the 50% differences in the estimated glucokinase activity levels. Furthermore, the correlation uncovered by Brocklehurst et al. (4) between small molecule glucokinase activator and lactate kinetics leaves us hopeful that our estimate of glucokinase activity is correlated or a "relative" measure of in vitro glucokinase activity. Currently, we are engaged in studies that will allow us to directly compare the in vitro and in vivo estimates of various parameters of the model pertaining to glucose- and lactate-shared metabolic pathways.

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DOI: 10.2337/dc12-1253
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Acknowledgments—No potential conflicts of interest relevant to this article were reported.

References

1. Agius L. Comment on: Stefanovski et al. Estimating hepatic glucokinase activity using a simple model of lactate kinetics. Diabetes Care 2012;35:1015–1020 (Letter). Diabetes Care 2012;35:e90. DOI: 10.2337/dc12-0786
2. Stefanovski D, Youn JH, Rees M, et al. Estimating hepatic glucokinase activity using a simple model of lactate kinetics. Diabetes Care 2012;35:1015–1020
3. Iozzo P, Lautamaki R, Geisler F, et al. Non-esterified fatty acids impair insulin-mediated glucose uptake and disposition in the liver. Diabetologia 2004;47:1149–1156
4. Brocklehurst KJ, Payne VA, Davies RA, et al. Stimulation of hepatocyte glucose metabolism by novel small molecule glucokinase activators. Diabetes 2004;53:535–541

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